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Efficient Synthesis of Cyclopropane Fused Heterocycles with Bromoethylsulfonium Salt


Dedication ((optional))

The 3-azabicyclo[3.1.0]hexane is a common motif in natural products.[1-6] Furthermore, this rigid framework represents a privileged class of pharmacologically active compounds, often showing enhanced binding affinities with their targets (Figure 1).[7] These bicyclics also represent conformationally restricted analogues of piperidines (e.g., trovafloxacin).[8] When substituted with a carboxylic acid moiety, they resemble conformationally restricted analogues of glutamate, gamma-amino butyric acid (GABA) or α/β-proline analogues (Figure 2).[9]

Numerous methods have been developed for the construction of azabicyclo[3.1.0]hexanes.[10] These include the Kulinkovich/de Meijere reaction,[11,12], cyclisation of tethered amines with metals (Pd,[13], Ru,[14], Rh,[15], Ag,[16]), cyclisation of tethered cyclopropanes,[17], and the Simmons-Smith/[18]/Corey-Chaykovsky/[19]/sulfur ylide-Au[20] cyclopropanations. These methods are usually only effective in the synthesis of one specific type of scaffold.

We were keen to develop a general strategy that could deliver 3-azabicyclo[3.1.0]hexanes with a range of functional groups in a range of positions. Our design plan for the synthesis of the scaffold was to effect a tandem process initiated by conjugate addition of an unsaturated amine 1 to vinyl sulfonium salt 2, generated in situ from the stable and crystalline salt 3 (Scheme 1). The intermediate sulfur ylide 4 would undergo intramolecular addition to the Michael acceptor to give a sulfonium enolate 5 which would ring close to the cyclopropane 6.

![Figure 1. Selected examples of important bicyclo[3.1.0]hexanes.](image1)

![Figure 2. Conformationally restricted scaffolds discussed in this work.](image2)

This tandem process is related to the previously described reactions that bear aldehydes or imines in place of Michael acceptors, giving fused bicyclic epoxides and aziridines respectively.[21,22] However, the more complex reaction with
Our studies began with the preparation of a diverse array of allylic amines. The allylic amines 1a-g were prepared in one step using either cross-metathesis\textsuperscript{24} or Wittig chemistry. Similarly, 1h-j were synthesized in two steps from commercially available amino acid-derived methyl esters through a DIBAL-H reduction/Wittig reaction sequence. Allylic amines 1k, and 1l with the appropriate protecting groups required several steps\textsuperscript{25} whilst 1m was available in one step from reaction of dihydrocinnamaldehyde with a vinylchromium nucleophile\textsuperscript{26} (see SI for details).

The reaction of unsaturated amide 1a with the stable and crystalline salt 3 was initially tested. After optimisation of the process (see supporting information) a set of conditions were established (method A), that led to moderate-high yields of the [3.1.0] bicycles with complete diastereoselectivity (Table 1).\textsuperscript{27} For example, unsaturated amide 1a gave the cyclopropane 6a in 62% yield as a single diastereomer. The Michael acceptors tested bore a range of electron-withdrawing groups, including Me and tBu esters, ketones, amides and nitriles (6a–6e). Furthermore, in the case of the unsubstituted allylic amide, the N-Cbz carbamate 1f\textsuperscript{28} could also be employed in place of the tosyl protecting group leading to the pyrrolidine 6f. The piperdine 6g was also accessible using the same process and again was formed with complete diastereoselectivity.

The method was further extended to a range of α-substituted allylic amines (1h–1m), although in this case NaH was found to be superior to DBU (method B). With a small substituent (Me, 1h), the azabicyclo[3.1.0] hexane 6h was formed with low diastereoselectivity but with larger substituents (1i, 1j) the adducts (6i, 6j) were formed with essentially complete diastereoselectivity. In terms of the N-protecting group, with α-substituted allylic amines, it was not possible to use the Cbz or Boc groups, but the more easily cleavable Cbz carbamate 1k could also be used and gave the tetrahydrofuran 6m, again with high selectivity. The methodology readily lent itself to the preparation of enantiomeric products, as illustrated with 6k, 6l, since the α-substituted allylic amines are easily obtained from chiral amino acids (serine in this case).

Expanding this methodology further, we were able to utilise easily accessible aza-Morita-Baylis-Hillman adducts 7a–7e\textsuperscript{29} (one step from the acrylate), as starting materials for the cyclisation. These reactions now lead to the formation of β-proline-derived fused cyclopropanes 8a–8e (Table 2).\textsuperscript{30}

Whilst unsaturated esters 7a and 7b worked well, giving the corresponding adducts 8a and 8b, respectively, in high yield and very high diastereoselectivity, unsaturated ketone (7c) behaved differently. In this case the major product was the epoxy-annelation adduct 9. Evidently, after 1,4-addition of the amide 7c to the vinyl sulphonium salt 1, the ylide intermediate reacts in a more favoured 6-exo-trig mode with the ketone moiety, rather than the desired 6-endo-trig mode with the alkene. Nevertheless, the pyrrolidine 8c was formed with high diastereoselectivity as before. The methodology readily lends itself to asymmetric synthesis, since the aza-Morita-Baylis-Hillman adducts 7a, 7b are obtainable using asymmetric organocatalysis.\textsuperscript{31} This was illustrated in the use of (+)-7a (82% ee), which gave the [3.1.0] bicycle (+)-8a without measurable racemization, which was increased to >99% ee after recrystallization.
Table 2: Reactivity of (aza)-Morita-Baylis-Hillman adducts.

<table>
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<tr>
<th>Adduct</th>
<th>Product</th>
<th>Yield</th>
<th>DR</th>
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<tbody>
<tr>
<td>3Ph3N</td>
<td>10a</td>
<td>72%</td>
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Scheme 4. Oxidation to $\alpha,\beta$-amino acid derivative 12.

The synthetic utility of the methodology is illustrated through a range of functional group transformations of several of the [3.1.0] pyrrolidines. For example, oxidative cleavage of the Ph group in 8a gave pyrrolidine 13 which is both an $\alpha$- and a $\beta$-amino acid derivative (Scheme 4).

Deprotection and oxidation of 6f gave the conformationally locked glutamic acid analogue (Scheme 5).

Finally, pyrrolidine 6f was converted into $\alpha$-amino-3-azabicyclo[3.1.0]hexan-3-ium chloride 16, an intermediate used in the synthesis of trovafloxacin, a potent antibiotic.

In conclusion we have developed a novel, efficient and versatile route for the formation of cyclopropane-fused heterocycles from easily available starting materials. In comparison to previous methods, this protocol enables the synthesis of a more diverse range of substituted and functionalized [3.1.0] scaffolds with very high diastereoselectivity. There is considerable interest in exploring this class of bioactive compounds, which should now be enabled by the methodology described herein.

**Experimental Section**

A stirred solution of amine or alcohol 1 (1.0 equiv.) and diphenyl bromoethyl sulfonium salt 3 (2.0 equiv.) in anhydrous solvent (0.1 M) at room temperature under inert atmosphere was treated with base (3.5 equiv.) and stirred for the indicated time (until complete consumption of starting material was detected by
Keywords: heterocycles • cyclopropanes • sulfur ylides • amino acids • Baylis-Hillman


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**Nitrogen Heterocycles**

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Efficient Synthesis of Cyclopropane Fused Heterocycles with Bromoethylsulfonium Salt

*Lord of the Rings*: [3.1.0] Bicyclic ring systems were synthesized using bromoethylsulfonium triflate and easily available, amino acid/aza-Morita-Baylis-Hillman derived allylic amines. The simple transformation displays a very high degree of diastereoselectivity and enables access to a diverse range of densely substituted pyrrolidine-based bicycles, a class of biologically important scaffolds.

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